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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/695,600	10/28/2003	Dennis A. Steindler	7203-8	6329

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 11/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/695,600	STEINDLER ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the preliminary amendment filed October 28, 2003, canceling claims 1-29 and adding new claims 30-39. Currently, claims 30-39 are pending.

Claim Rejections - 35 USC § 101

35 U.S.C. § 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 37-39 are rejected under 35 USC §101, as directed to non-statutory subject matter. Claims 37-39 read on cells naturally present in the tissue of an animal subject, including animal CNS and brain tissue. In claims 37-39 a purified pluripotent brain stem cell may be returned to the *in vivo* environment from which it was originally derived, in unaltered form.

Claim Rejections - 35 USC § 112, written description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33 and 35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 33 and 35 encompass: (i) any mammalian pluripotent brain stem cell; (ii) any murine pluripotent brain stem cell.

The specification describes methods that can be used to isolate, amplify and grow stem/precursor cells from the brains of mouse and postmortem adult human (Examples I-III). However, the specification provides no cross-species analysis to demonstrate that such cells may be derived from other murine species, such as rat or gerbil. Moreover, Applicant's specification provides no examples of additional species for sources of Type I, II and III clones, to provide an adequate representation for mammals. As such, the Artisan of skill could not predict that Applicant possessed

any additional species, except for mouse and human. Hence, only cells or clones from mouse and human could be demonstrated as possessed.

> To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention (January 5, 2001 Fed. Reg., Vol. 66, No. 4, pp. 1099-11). MPEP §2163.

Applicant's attention is directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of (i) any mammalian pluripotent brain stem cell; (ii) any murine pluripotent brain stem cell at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated culture of multipotent, progenitor or precursor brain stem cells

containing sub-populations of cells that at different stages of differentiation express markers for glial fibrillary acidic protein, nestin and TuJ1, does not reasonably provide an enablement for a purified pluripotent brain stem cell as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404:

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

MPEP § 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection."

The Nature Of The Invention And Breadth Of Claims

Claims 30-32 are drawn to a purified, pluripotent brain stem cell that is immunonegative for GFAP, nestin and TuJ1 markers. Claim 33 further limits the pluripotent brain stem cell to a mammalian cell. Claims 34 and 35 narrow the mammalian pluripotent brain stem cell to human and murine respectively. Claim 36 is directed to a pluripotent brain stem cell "obtained from" a post-mortem animal subject. Claims 37-39 are directed to a pluripotent brain stem cell that has been introduced into a tissue of an animal subject. The term pluripotent as applied to stem cells is understood to mean : not fixed as to potential development and having development plasticity. A pluripotent stem cell has therefore the developmental potential to give rise to or differentiate into any number of different cell types and tissue morphologies. Because these claims encompass a wide range

of conditions and phenotypes associated with a number of different differentiated cell types, under several biological conditions, the detail of the disclosure provided by Applicant, in view of the prior art, must encompass a wide knowledge, so that one of skill in the art, at the time of invention by Applicant (hereafter the "Artisan"), would be able to practice the invention as claimed by Applicant, without undue burden being imposed on such Artisan. This burden has not been met because it would require undue experimentation to produce a purified pluripotent brain stem cell that is immunonegative for GFAP, nestin and TuJ1, as claimed in the instant application.

The Unpredictability Of The Art And The State Of The Prior Art

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The state of the prior art is effectively summarized by the references of Weiss et al. (U.S. Patent No. 5,851,832; filed Jun. 7, 1995); Boss et al.(U.S. Patent No. 5,411,883; filed Aug. 12, 1992); Johe (U.S. Patent No. 5,753,506; filed Aug. 12, 1992); Gage et al. (Ann. Rev. Neurosci. 18:159-192; 1995); Reynolds et al. (Dev. Biol. 175:1-13; 1996) and Laywell et al. (Neurosci. Abs. 232:297, 1997).

The art teaches the feasibility for the isolation and propagation of multipotent neural stem cells that under certain culture conditions may undergo subsequent differentiation into glia, astrocytes and neurons (Weiss, Example 20, second paragraph) . However, the art also teaches that the resulting differentiated phenotypes and morphological properties resulting from a population of multipotent neural stem cells is dependent upon isolation and culturing conditions and is highly unpredictable (Gage et al., pp. 174-175). Further, at the time of the invention, the art teaches methods for obtaining a population of cells that may be enriched in multipotent neural stem cells (Weiss, columns 10 and 11), but does not teach a purified pluripotent brain stem cell.

The instant claims are drawn to a broad phenotype of a purified cell that is not apparent from the disclosure of the invention. In view of the lack of teachings or guidance provided by the specification with regard to an enabled, purified pluripotent brain stem cell, the lack of teachings or guidance provided by the specification to overcome the art-recognized unpredictability and difficulty inherent in isolation of purified stem cell, and the lack of correlation between the multipotent cells of the present invention and a pluripotent brain stem cell as claimed, and for the specific reasons cited

above, it would have required undue experimentation for an Artisan of skill to make and use the claimed invention. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

The Amount Of Direction Or Guidance Presented And Working Examples

The specification fails to disclose adequate representations of a purified pluripotent brain stem cell. The specification provides for the culture of type I cells obtained from mouse and human brain tissue following dissociation. The specification outlines the culture conditions and concludes: "some type II cells are also present in these cultures" (Example 1, last paragraph). The production of type II clones and the relevant culture conditions are disclosed in Example 2. The type II culture clones are described as containing dense debris for 10-14 days and further, that some type III clones were present. Example 3 teaches conditions for the differentiation of type III clones neurons or glia, but not any additional cell types. Examples 1, 2 and 3 of the specification teach that there is a continuum of cell differentiation, which in part is dependent on the cell culture conditions. Further, Example 5 teaches that EM analysis of type II clones revealed rings of small, tightly apposed cells that often surround a core of flocculent, non-cellular material having many of the characteristics of extracellular matrix (second paragraph).

The guidance provided by the specification amounts to an invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses a subset of culture conditions that can give rise to a mixed population of multipotent brain-derived neuronal stem cells.

Quantity Of Experimentation

The quantity of experimentation in this area is extremely large, as there are a significant number of parameters, which would have to be studied and tested to make and definitively show that one is in possession of a purified pluripotent brain stem cell. This would require a significant degree of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level Of Skill In The Art

The level of skill in the art at the time of invention is deemed to be high. However, because of the immaturity of the art, and its unpredictability, as shown by the other factors, one of skill in the art at the time of invention by Applicant would not have been able to make and/or use the invention claimed without undue experimentation.

Analysis And Conclusion

Applicant is therefore enabled for an isolated culture of multipotent, progenitor or precursor brain stem cells containing a sub-population of cells that are immunonegative for glial fibrillary acidic protein, nestin and TuJ1 (Type I clones), wherein said culture is capable of differentiation into Type II and Type III clones, that positively display markers for glial fibrillary acidic protein, nestin and TuJ1. In the instant case, as discussed above, in a highly unpredictable art where the generation of a **purified pluripotent** brain stem cell, encompassing numerous possible physiological alterations that may give rise to a multitude of tissue types, together with the large quantity of research required to define these unpredictable variables, and the lack of guidance provided in the specification, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 30-33, 35 and 37-38 are rejected under 35 USC § 102(b) by Boss et al. (of record). Claims 31 and 32 are product by process claims, and as such, are directed to the stem cell. Boss et al.

teach the isolation and culture of a population of neuron progenitor cells obtained from mammalian brain in a first culture medium, that when cultured in a second culture medium, proliferate the neuron progenitor cells ((paragraph 5, column 4). Further, the neuron progenitor cells can be induced to differentiate *in vitro* (column 13 and Example 6, column 18). Boss et al. also teach a method for transplanting neuron progenitor cells into the brain of a host animal (column 14, second paragraph). As there are no distinguishing features between the enabled invention of the instant claims and the taught population of stem/progenitor cells, the cells and the subsequent transplanting of Boss et al. anticipate the claimed invention.

Claims 30-39 are rejected under 35 USC § 102(e) by Johe et al. (of record). Johe et al. teach the isolation and culture of a population of multipotential stem cells from embryonic and adult mammals, that can be directed to differentiate into neurons, oligodendrocytes and astrocytes (Abstract and column 13 line 1 to column 16, line 3). As there are no distinguishing features between the enabled invention of the instant claims and the taught population of stem/progenitor cells, the cells and the subsequent transplanting of Boss et al. anticipate the claimed invention.

Claims 30-33 are rejected under 35 USC § 102(e) by Weiss et al. (of record). Weiss et al. teach the isolation and culture of a population of neural stem/progenitor cells from embryonic and adult mammals, including human embryonic or adult brain (post-mortem human brain tissue is described in Example 9). The population of neural stem/progenitor cells is expanded in culture and is largely composed of undifferentiated cells (column 36, lines 4-6; Examples 1, 2, 4, 5, 9 and 11). The stem cells can differentiate into neurons and glial cells (Examples 7 and 8)Weiss et al. also teach the transplantation of multipotential neural stem cells in animal models (Example 45). As there are no distinguishing features between the enabled invention of the instant claims and the taught population of stem/progenitor cells, the cells and the subsequent transplanting of Weiss et al. anticipate the claimed invention.

Conclusion

No claims allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst Victor Barlow, whose telephone number is **(571) 272-0506**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(571) 272-3311**. The examiner can normally be reached Monday through Friday, between 7:00 am-4:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on **(571) 272-0731**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

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